Thrombosis and Coagulopathy in COVID-19 Patients Requiring Extracorporeal Membrane Oxygenation

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The coronavirus disease 2019 (COVID-19) pandemic has challenged intensivists caring for patients with severe respiratory disease, associated multiorgan dysfunction, and high mortality.[1] Extracorporeal membrane oxygenation (ECMO) has been used to manage patients with COVID 19-associated severe respiratory or cardiac failure with mortality in excess of 50%.[2,3] A significant feature of this disease appears to be an excess of thrombosis and there have been reports of an incidence of more than 30% of intensive care unit (ICU) admissions.[4] The etiology of thrombosis in this setting may be closely linked with the hyperinflammatory response of the immune system when exposed to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[5] In addition, there is early development of a disseminated intravascular coagulation (DIC)-like picture in a subset of patients, the management of which is made more complicated if providing systemic anticoagulation to prevent thrombosis and maintain the extracorporeal circuit. The purpose of this editorial is to briefly discuss COVID-19-associated procoagulant and anticoagulant states in the context of ECMO support.

Thrombosis in COVID-19

SARS-CoV-2 infection shares pathophysiological characteristics with other coronaviruses (severe acute respiratory syndrome and Middle East respiratory syndrome). The initial manifestation of the infection is characterized by endotheliopathy and pulmonary vascular microthrombosis, which may present with hypoxemia and a need for oxygenation or ventilatory support. Endotheliopathy activates two independent molecular pathways: inflammatory and microthrombotic.[4–7] The former pathway triggers the release of inflammatory cytokines and the latter promotes exocytosis of unusually large von Willebrand factor multimers (ULVWF) and platelet activation. The inflammatory pathway initiates inflammation, but the microthrombotic pathway produces "microthrombi strings" composed of platelet-ULVWF complexes, which become anchored on the injured endothelial cells and trigger disseminated intravascular microthrombosis.[4–7]

High plasma levels of proinflammatory cytokines (interleukin-1, 2, 6, and 7, granulocyte colony-stimulating factor and tumor necrosis factor-α) have been observed in COVID-19 patients admitted to ICU. This is consistent with, although not diagnositic of, a "cytokine storm" associated with the secondary development of a hemophagocytic lymphohistiocytosis.[8] This contributes to fibrinogen generation and an overwhelming of the profibrinolytic pathway causing increased expression on plasminogen activator inhibitor-1.[9] A recent postmortem evaluation of 10 COVID-19 patients reported the presence of diffuse alveolar damage and fibrin–platelet thrombi in small arteries in the lungs and other organs.[10] However, the generalizability of these findings to a wide range of COVID-19 patients is unclear.

This initial prothrombotic insult and inflammation in combination with other risk factors including immobility, obesity, and hypovolemia may contribute to an increased incidence of arterial and venous thromboembolism.[9]

There are reports of deep vein thrombosis, pulmonary emboli, ECMO cannula, and circuit thrombosis and ischemic strokes among others.[4,9] This could potentially have a contributory effect on the severity of respiratory failure and consequently multiorgan failure. A lack of resolution of the widespread thrombi may be an important factor in the prognosis of COVID-19 patients in ICU and various studies in patients with COVID-19 have consistently shown a strong association between elevated D-dimer levels and adverse overall outcomes.[8,11] Although this association is real, it remains uncertain whether the mechanistic explanation of the links between elevated D-dimer levels and outcomes in this context is increased fibrin generation and degradation or hyperinflammation.[8,11,12]

The Extracorporeal Circuit, COVID-19, and Bleeding

COVID-19-associated coagulopathy (CAC) has been recently described and shares similarities with classic DIC. The degree of activated partial thromboplastin time elevation in CAC is often less than prothrombin time (PT) elevation (likely due to elevated factor VIII levels), thrombocytopenia is usually mild (approximately 100×10^9/L), and microangiopathy is not present.[13,14] In most patients, overt bleeding is not evident with only mild derangements in the usual laboratory tests of coagulation, which do not fulfil usual clinical definition of

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coagulopathy.[15] However, the patients with the worst outcomes have early coagulopathy, raised PT, and increased D-dimer.[14] A review of the coagulation profile of 183 hospitalized patients revealed a median onset of DIC at 4 days in over 70% of the nonsurvivors while only 1 of the 78 survivors had evidence of DIC.[15]

One of the most common late complications of ECMO support in COVID-19 patients is bleeding, which has been associated with poor outcomes, albeit with very limited data.[3,16] Given the context described above, it is possible that any coagulopathy associated with the extracorporeal circuit would have a synergistic effect with CAC, although there is currently little evidence to support this.

The initial effect of establishing ECMO creates an overall procoagulant effect.[17,18] There is contact activation of the coagulation cascade, thrombin generation, and fibrin deposition on the artificial surfaces.[17,18] There is also an inflammatory response at initiation of extracorporeal support, which leads to upregulation of prothrombotic pathways and, to a lesser degree, the fibrinolytic pathways.[17–21] This underscores the role of anticoagulation in maintaining circuit patency; however, given the dynamic nature of the extracorporeal support, the coagulation state is also dynamic. As the ECMO support proceeds, the anticoagulant factors have an increased influence due to loss of large-molecule von-Willebrand factor and decreased platelet adhesion (due to glycoprotein 1b and glycoprotein VI loss), which may increase bleeding risk.[19–22] In addition, there is consumption of coagulation factors and reduction in the effect of contact activation over time as protein adsorption to the artificial surfaces develops.[23] In most patients, the procoagulant effects predominate hence the need for continued anticoagulation.[23]

It is well established that the significant inflammation associated with sepsis can alter this balance by initially producing an aggravated prothrombotic response at the start of extracorporeal support with consequent rapid transition to an anticoagulant state, characterized by a DIC-type picture and hyperfibrinolysis (**Figure 1**). This state is associated with an increased risk of death.[24] The hyperinflammatory state associated with COVID-19 disease may create these effects as well, potentially contributing to hemorrhagic complications encountered during ECMO support.[16]

Hemorrhage in this context is very difficult to manage as the circuit remains prothrombotic while the patient is bleeding.[23] Given the complex nature of this problem, early consultation with hematology may be prudent as part of a multidisciplinary team approach.

This effect has practical implications when caring for COVID-19 patients requiring ECMO support. The varying and dynamic heparin requirements can be difficult to monitor and manipulate. Thrombotic complications such as acute pulmonary embolism, ECMO cannula thrombosis and oxygenator thrombosis have been reported in COVID-19 patients requiring ECMO.[25] Higher rates of bleeding are encountered when procedures are carried out with attendant increased use of blood products. Some have suggested that planned invasive procedures (e.g., percutaneous tracheostomy) should be performed in the early procoagulant phase, preferably in the first 48–72 hours of the ECMO run, especially in patients with early evidence of CAC.[26] However, evidence for this is lacking. In the case of necessary emergency procedures, the increased risk of bleeding and its effect on outcomes must be strongly considered when making a risk-to-benefit judgment, especially in patients who are late into their ECMO support.

Conclusion

COVID-19 presents with a hyperinflammatory immune reaction in patients requiring intensive care and extracorporeal support. The associated increased risk of thrombosis and coagulopathy in ECMO patients is a result of a combination of processes driven by the disease occurring in synergy with the effect of the extracorporeal circuit on the coagulation system. Large-scale prospective data on hemorrhagic and thrombotic

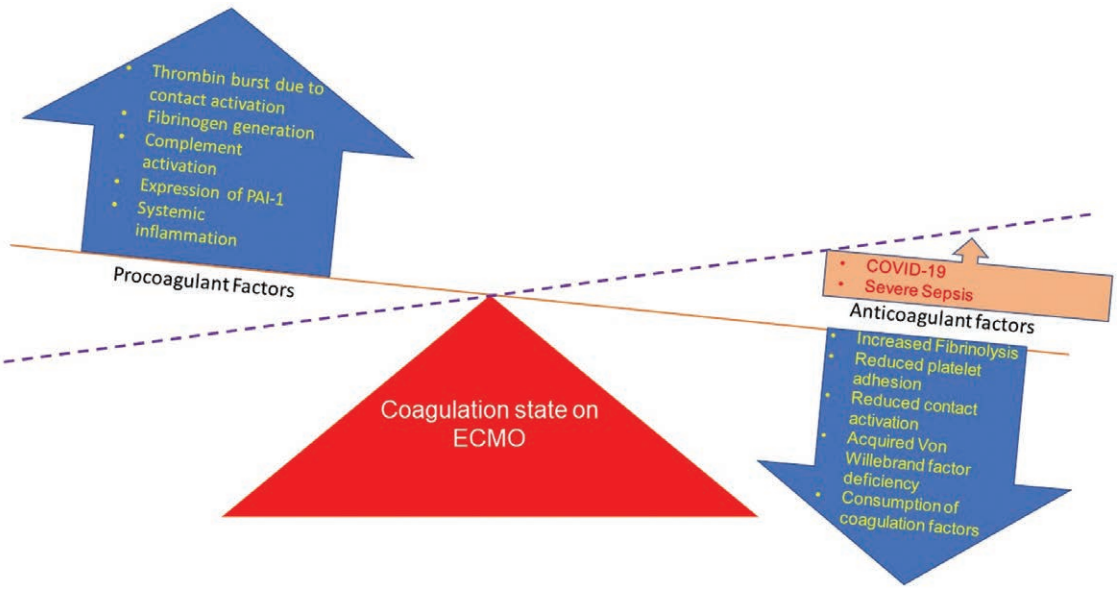

Figure 1. Effect of a hyperinflammatory state on coagulation in patients receiving extracorporeal membrane oxygenation (ECMO). COVID-19, novel coronavirus disease 2019; PAI-1, plasminogen activator inhibitor-1.

complications in the COVID-19 patient population requiring ECMO support may provide insights into these pathophysiological processes and the effective management strategies. Ongoing analysis of the Extracorporeal Life Support Organization registry data and data from ECMO centers around the world (ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCard study) will hopefully help to better characterize and understand these pathologic derangements of coagulation.[27]

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